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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/773,000
Filing Date: February 05, 2004
Appellant(s): SOOD ET AL.

Yonggang Ji
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/14/2008 appealing from the Final Office action mailed 9/14/2007 and the advisory action of January 31, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The copy of the appealed claims contained in the Appendix to the brief is correct.

5,656,462	Keller	08-1997
5,683,875	Lichenwalter	11-1997
5,821,095	Hattori	10-1998
5,112,960	Bronstein	05-1992
WO/2001/094609	Williams	12-2001

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31 and 32-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP 2163.06 notes “If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).”

The MPEP states in 2173.05, " Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement."

Claims 1-31 recite "detectable species without first separating by charge of said detectable species from the reaction mixture" and claims 32-56 recite "detecting said labeled polyphosphate without first separating by charge of said labeled polyphosphate from the reaction mixture" which appear to be new matter. The specification does not provide basis for detection without separation based on charge. The response of 7/2/2007 denotes this amendment has been made to overcome the art of record however, does not distinctly point out basis for the amendment. The specification does not appear to recite or suggest this limitation anywhere. Thus this is considered new matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 9, 11-18, 20-23, 27-38, 40, 42-45, 47, 49-50, 55, 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al (WO/2001/94609). With regards to claim 1, Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single

molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a g-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "The use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is a continuing polymerization assay by adding different nucleoside polyphosphates.

With regards to claim 2, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21). Target nucleic acid is a template.

With regards to claim 3, Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19). Williams teaches oligonucleotides are primers (see page 29, lines 7-18).

With regards to claim 4, Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2).

With regards to claim 5, Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6).

With regards to claim 6, Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29).

With regards to claim 7, Williams teaches, “the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated” (see page 25, lines 15-16). The amount of pyrophosphate released is thus proportional to the amount of template nucleic acid present. The amount of nucleic acid present is thus quantitated.

With regards to claim 9, Williams teaches a nucleic acid polymerase (see page 4 lines 20-21).

With regards to claims 11 and 12, Williams teaches DNA as a template (see abstract). Instant specification teaches, “’oligonucleotide’ includes linear oligomers of nucleotides or derivatives thereof, including deoxyribonucleosides.” Oligonucleotide thus encompasses DNA.

With regards to claim 13, Williams teaches sequencing in real time (see abstract). Real time sequencing requires the conducting step and subjecting step to be done simultaneously.

With regards to claim 14, Williams et al teaches the figure at the top of page 15 Williams further teaches in line 21 of page 20, Y can be 0, 1, or 3. Williams thus teaches a polyphosphate with 5 phosphates (2 in the figure plus the 3 of the y

depiction). Williams thus teaches 4 or more phosphate groups in the polyphosphate chain.

With regards to claim 15, Williams teaches, “the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated” (see page 25, lines 15-16). As Williams teaches the pyrophosphate has the detectable label, this is a detectable species directly proportional to mount of nucleic acid sequence.

With regards to claim 16, Williams teaches the use other phosphate transferring enzymes that include ATP sulphurylase-luciferase system and phosphatase.

With regards to claim 17, Williams teaches the use of four deoxynucleotide triphosphates, each labeled with a different color fluorescent dye (see page 24, lines 5-6).

With regards to claim 18, Williams teaches the nucleotide sequence of the target DNA can be thereafter be directly read from the order of releases dyes attached to pyrophosphate (see page 24, lines 7-8).

With regards to claim 20, Williams teaches use of fluorescent dyes and chromogenic dyes (see page 16, line 4 and page 24, lines 5-6).

With regards to claim 21 Williams teaches the molecule of the figure on top of page 15. Williams teaches the B is a nucleobase, a sugar moiety is depicted, three phosphates are depicted (the Y in the figure is in line 21 suggested to be , 0, 1, or 3) and the f is a label that can be independently detected upon activation (cleavage).

With regards to claim 22, Williams teaches the use of fluorescent dyes (see page 16, lines 15-23).

Claim 23 encompasses resorufin phosphate.

With regards to claim 23, Williams teaches the use of resorufin (see page 16, line 16). The incorporation of resorufin into the polyphosphate complex of Williams would result in resorufin phosphate or derivatives thereof.

With regards to claims 27 and 28, Williams teaches the use of a nucleoside linked to a pentose at the 1' position, including the 2'-deoxy and 2'-hydroxyl form (see page 8, lines 21-25). Williams et al thus teaches the use of a ribosyl or 2'deoxyribosyl sugar.

With regards to claim 29, Williams et al teaches use of adenine, guanine, cytosine, uracil, thymine, deazaadenine and deazaguanosine. Williams thus teach nitrogen-containing heterocyclic bases.

The addition of terminal phosphate labeled polyphosphates in claims 30 and 31 is interpreted as the incorporation into primer elongation.

With regards to claims 30, 31, 55 and 56, Williams teaches sequencing the target nucleic acid (see page 4, lines 28-29). Sequencing is based on the addition of nucleotides or nucleoside polyphosphates in order to make a complementary strand of the target region. The sequencing method taught by Williams encompasses this, further Williams teachings of the use of four deoxynucleotide triphosphates, each labeled with a different color fluorescent dye (see page 24, lines 5-6) results in sequencing by addition of labeled bases.

With regards to claim 32, Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a

single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams et al teaches the figure at the top of page 15

Williams further teaches in line 21 of page 20, Y can be 0, 1, or 3. Williams thus teaches a polyphosphate with 5 phosphates (2 in the figure plus the 3 of the y depiction). Williams thus teaches 4 or more phosphate groups in the polyphosphate chain.

With regards to claim 33, Williams teaches immobilizing a target nucleic acid onto a solid support (see page 4, lines 20-21). Target nucleic acid is interpreted as template.

With regards to claim 34, Williams teaches oligonucleotides can be immobilized on a solid support (see page 9, lines 16-19). Williams teaches oligonucleotides are primers (see page 29, lines 7-18).

With regards to claim 35, Williams teaches immobilizing a nucleic acid complex onto a solid support, contacting the polymerase and detecting release of pyrophosphate (see page 21, line 30 to page 22 line 2).

With regards to claim 36, Williams teaches immobilizing a nucleic acid polymerase on a solid support for conducting (see page 4, lines 5-6).

With regards to claim 37, Williams teaches a flowcell having an inlet port and an outlet port (page 4, line 29).

With regards to claim 38, Williams teaches, "the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated" (see page 25, lines 15-16). The amount of pyrophosphate released is thus proportional to the amount of template nucleic acid present. The amount of nucleic acid present is thus quantitated.

With regards to claim 40, Williams teaches a nucleic acid polymerase (see page 4 lines 20-21).

With regards to claims 42 and 43, Williams teaches DNA as a template (see abstract). Instant specification teaches, "'oligonucleotide' includes linear oligomers of nucleotides or derivatives thereof, including deoxyribonucleosides." Oligonucleotide thus encompasses DNA.

With regards to claim 44, Williams teaches, "the amount of pyrophosphate released which, in turn, is directly proportional to the amount of base incorporated" (see page 25, lines 15-16). As Williams teaches the pyrophosphate has the detectable label,

this is interpreted as detectable species directly proportional to mount of nucleic acid sequence.

With regards to claim 45, Williams teaches the use of four deoxynucleotide triphosphates, each labeled with a different color fluorescent dye (see page 24, lines 5-6).

With regards to claim 47, Williams teaches use of fluorescent dyes (see page 24, lines 5-6).

With regards to claim 48, Williams et al teaches the figure at the top of page 15 Williams further teaches in line 21 of page 20, Y can be 0, 1, or 3. Williams thus teaches a polyphosphate with 5 phosphates (2 in the figure plus the 3 of the y depiction). Williams thus teaches 4 or more phosphate groups in the polyphosphate chain.

With regards to claim 49, Williams teaches use of fluorescent dyes and chromogenic dyes (see page 16, line 4 and page 24, lines 5-6).

With regards to claim 50, Williams et al teaches xanthenes, cyanine, coumarin and BODIPY dyes (see page 16, lines 15-22). Williams thus teaches the fluorescent dyes recited.

With regards to claim 50 and 51, Williams teaches the molecule of the figure on top of page 15. Williams teaches the B is a nucleobase, a sugar moiety is depicted, three phosphates are depicted (the Y in the figure is in line 21 suggested to be , 0, 1, or 3) and the f is a label that can be independently detected upon activation (cleavage).

With regards to claims 52 and 53, Williams teaches the use of a nucleoside linked to a pentose at the 1' position, including the 2'-deoxy and 2'-hydroxyl form (see page 8, lines 21-25). Williams et al thus teaches the use of a ribosyl or 2'deoxyribosyl sugar.

With regards to claim 54, Williams et al teaches use of adenine, guanine, cytosine, uracil, thymine, deazaadenine and deazaguanosine. Williams thus teach nitrogen-containing heterocyclic bases.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 8 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Wittwer et al (US Patent 6174670). Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when

the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams does not teach quantifying nucleic acid by comparing spectra with a known standard.

However, Wittwer teaches determining the concentration of a nucleic acid by comparison to the fluorescence of a known concentration template (see column 11, line 65 to column 12 line 40). Wittwer teaches this simple method allows quantification of low copy number DNA (see column 39, lines 59-60).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to quantitate the nucleic acid sequences of Williams with Wittwers method of quantitation, because Wittwer teaches it is a simple method for quantification of low copy number DNA. The ordinary artisan would be motivated to improve Williams method of sequencing because Wittwer teaches a simple method for quantification of low copy number DNA.

Claim 10 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Keller et al (US Patent 5656462).

Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates.

Williams does not teach the use of an RNA template.

However, Keller et al teaches the use of an RNA template (see column 13, lines 54-55) because it is useful in the preservation and analysis of genes.

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to improve Williams method of sequencing by the use of RNA templates as taught by Keller, because Keller teaches use of RNA allows gene

analysis. The ordinary artisan would be motivated to use the RNA template, because Keller teaches the RNA template is useful in preservation and analysis of genes.

8. Claim 19 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Lichenwalter et al (US Patent 5683875). Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams teaches the use of four deoxynucleotide triphosphates, each labeled with a different color fluorescent dye (see page 24, lines 5-6). Williams does not teach the use of an antibody as a detection reagent.

However, Lichtenwalter et al teach the use of an antibody to detect elongated nucleic acid complexes (see column 3, lines 27-30, column 3, lines 14-17), because it is a convenient and reliable diagnostic method (column 13, lines 20-21).
Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to use the antibodies taught by Lichtenwalter to detect the elongation products of Williams, because Lichtenwalter teaches it is a convenient and reliable diagnostic method. The ordinary artisan would be motivated to detect Williams elongation products with Lichtenwalter's antibodies because Lichtenwalter teaches it is a convenient and reliable diagnostic method.

Claim 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Hattori et al (US Patent 5,821,095, Published October 13, 1998).

Claim 23 is being rejected as directed to 4-methylumbelliferyl phosphate. Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable

moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams teaches the molecule of the figure on top of page 15. Williams teaches the B is a nucleobase, a sugar moiety is depicted, three phosphates are depicted (the Y in the figure is in line 21 suggested to be , 0, 1, or 3) and the f is a label that can be independently detected upon activation (cleavage). Williams does not teach the use of chromogenic dyes 5-bromo-4-chloro-3-indolyl phosphate, 3-indoxyl phosphate, p-nitrophenyl phosphate and derivatives thereof (claim 24), 4-methylumbelliferyl phosphate (claim 23) or 1,2 doixetane (claim 25). However, Hattori et al teaches the use of p-nitrophenyl phosphate, 5-bromo-4-chloro-3-indolyl phosphate, 4-methylumbelliferone phosphate and chemiluminescent dioxetanes in phosphatase assays (see column 1, lines 53-57). Hattori et al further teaches these substrates allow for a significant improvement in sensitivity of the phosphatase assay. Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the substrates of Hattori et al in the method of Williams. One of ordinary skill in the art would be motivated to use Hattori et al substrates, because Hattori et al teaches they result in more sensitive detection.

Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (WO/2001/94609) in view of Bronstein et al (US Patent 5,112,960 Issue May 12, 1992).

Williams teaches,"(a) immobilizing a complex comprising a nucleic acid polymerase, or a target nucleic acid onto a solid support in a single molecule configuration; b) contacting the complex with a sample stream comprising a target nucleic acid when the polymerase is immobilized, or a polymerase when the target nucleic acid is immobilized, a primer nucleic acid which complements a region of the target nucleic acid of the region to be sequenced; and a labeled nucleotide phosphate (NP) having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer nucleic acid wherein the solid support is disposed in a flowcell having an inlet port and an outlet port; detecting the charged detectable moiety, thereby sequencing the target nucleic acid" (see page 4, lines 20-29). Williams teaches, "NP probe is a nucleotide triphosphate (NTP), and the terminal phosphate is a y-phosphate with a fluorophore moiety attached" (See page 3, lines 14-15). Williams further teaches, "the use of a phosphatase enhances the charge-switch magnitude by dephosphorylating the PPi-F" (see page 25, lines 12-13). The sample stream taught by Williams is interpreted as continuing polymerization assay by adding different nucleoside polyphosphates. Williams teaches the molecule of the figure on top of page 15. Williams teaches the B is a nucleobase, a sugar moiety is depicted, three phosphates are depicted (the Y in the figure is in line 21

suggested to be , 0, 1, or 3) and the f is a label that can be independently detected upon activation (cleavage).

Williams et al does not teach the use of chemiluminescent compounds 1,2-dioxetane or the compounds 2-chloro-5-(4-methoxyspiro[1,2-dioxetane-3,2'-(5-chloro-)tricyclo [3,3,1 - 13,7]_decan]_ 1 -yl)- 1 -phenyl phosphate, chloroadamant-2' -ylidenemethoxyphenoxy phosphorylated dioxetane, 3-(2'-spiroadamantane)-4-methoxy-4-(3"-phosphoryloxy)phenyl-1,2-dioxetane and derivatives thereof .

In addition, the court have stated:

similar properties may normally be presumed when compounds are very close in structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972) (see MPEP 2144.08(d)).

The teachings of Bronstein et al in the structure of the abstract is a derivative of the recited compounds. Bronstein teaches the compounds of her invention allow for the studying of chemical or biological substances (including nucleic acids) to allow structures to be determined and quantified (see column 2, lines 5-9). Bronstein et al

teaches her enzymatically cleavable 1,2 dioxetanes allow for quick detection and steady state light emission (see column 3, lines 7-10). Bronstein et al teaches that these compounds are cleavable by alkaline phosphatases and decrease the time necessary to conduct assays (see column 3, lines 25-28, column 4, lines 62-65). Bronstein et al further teaches these compounds provide for improved signal (see column 5, lines 3-8).

Therefore it would have been prima facie obvious to one of ordinary skill of the art at the time the invention was made to improve the method of pyrophosphatase sequencing taught by Williams by use of the 1,2-dioxetane taught by Bronstein. One of ordinary skill in the art would be motivated to use the 1,2 dioxetane compounds of Bronstein because Bronstein teaches it allows rapid detection and quantification. The ordinary artisan would also be motivated to combine the 1,2 dioxetanes of Bronstein and the method of Williams, because Bronstein teaches the 1,2 dioxetanes are cleavable by alkaline phosphatase (which are commonly used in pyrophosphate sequencing) and decrease the assay time. The combined teachings of Williams and Bronstein would result in a fast quantitative method of detecting the alkaline phosphatase activity of pyrophosphate sequencing.

(10) Response to Argument

112-1st paragraph rejection

The appellant asserts on pages 4-6 of the brief that the claims 1-56 are not properly rejected under 35 USC 112, first paragraph for failing to comply with the written description requirement.

It is noted that written description rejection is drawn to the limitation, “without first being separated by charge” (claim 1 and 32). The MPEP states in 2173.05, “Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.” Thus to demonstrate support for the limitation in the specification, “without first being separated by charge,” appellants must point to where the specification with teaches separation based on charge prior to detection or specifically excludes separation based on charge prior to detection. It is noted that the arguments of appellants are directed to the specification teaching that separation is not required, but does not provide support for separation based on charge.

The appellants assert that one of skill in the art provided with the specification could clearly understand in the claimed methods the labeled polyphosphate does not need to be separated by charge. However, the New Matter rejection is drawn to the specification not contemplating the narrowing of the claim by the recitation of " without first being separated by charge.”

The Appellant asserts support can be found at “the specification at page 4, lines 6-9, states, "The labeled polyphosphate then reacts with phosphatase or a phosphate or polyphosphate transferring enzyme to produce free label with a signal readily distinguishable from the phosphate bound dye’. Appellants submit that the phrase "readily distinguishable" clearly indicates that no separation is required.” The cited portion of the specification teaches that the cleaved labeled polyphosphate can be distinguished after phosphatase treatment. However this statement in the specification

does not teach that separation is not required or that applicants contemplated narrowing the scope of the claims to exclude separation based on charge. The specification has not defined “readily distinguishable” as being “without first being separated by charge”. The specification on the other hand, states, “readily distinguishable from other components due to a difference in mass” (see page 12, lines 4-6), which would indicate that the specification teaches separation, for example, based at least on mass, contrary to applicants assertion that specification supports written support for “ without first being separated by charge".

The response continues, “Later in the same paragraph (page 4, lines 12-14), the specification states that, "After sufficient time is allowed for the polymerization reaction, which may range from milliseconds to several minutes, and detecting the presence or absence of signal, solid support may be separated from solution..." The recited portions of the specification teach that the presence or absence of the signal can be detected following polymerization. Further the recited portion of the specification is drawn to removal of the solid support from the reaction mixture, while the new matter rejection is drawn to “detecting said detectable species without first separating by charge of said detectable species from the reaction mixture.” The cited portion of the specification does not provide support for a method that excludes separating the detectable species from the reaction mixture, but removing the template.

The response further asserts that the specification provides support for the, “detecting said detectable species without first separating by charge of said detectable species from the reaction mixture” on the top of page 12 of the specification. Page 12

of the specification teaches, “heterocyclic base; X is O, S, or NH; Y is O, S, or BH3; and L is a phosphatase activatable label which may be a chromogenic, fluorogenic, chemiluminescent molecule, mass tag or electrochemical tag. A mass tag is a small molecular weight moiety suitable for mass spectrometry that is readily distinguishable from other components due to a difference in mass. An electrochemical tag is an easily oxidizable or reducible species. It has been discovered that when n is 2 or greater, the nucleotides are significantly better substrates for polymerases than when n is 1. Therefore, in preferred embodiments, n is 2, 3 or 4, R1 and R2 are independently H or OH; X and Y are O; B is a nucleotide base and L is a label which may be a chromogenic, fluorogenic or a chemiluminescent molecule”. Page 12 describes several different labels, however the cited portions of page 12 do not demonstrate that at time of filing the applicant had contemplated narrowing the scope of the invention to where detectable species are detected without first separating them based on charge from the reaction mixture.

The Appellants further assert support for amending claim 32 to recite,” detecting said labeled polyphosphate without first separating by charge of said labeled polyphosphate from the reaction mixture” can be found on page 13, lines 25-33, which teach, “in embodiments including terminal- phosphate-labeled nucleotides having four or more phosphates in the polyphosphate chain, it is within the contemplation of the present invention that the labeled polyphosphate by-product of phosphoryl transfer may be detected without the use of phosphatase treatment ....Upon incorporation of the nucleoside monophosphate, the label polyphosphate by-product may be detected due

to its enhanced fluorescence." While the cited portion of the specification provide support that applicant's had contemplated detecting without the use of phosphatase, however the cited portions do not teach or suggest detection without separation of the cleaved polyphosphate based on charge from the reaction mixture.

The appellants further assert, "the specification taking as a whole, clearly describes sequencing methods which do not require a separation step, prior to the detecting step, of either the detectable species or the labeled polyphosphate from the reaction mixture." The portions of the specification cited in the appeal brief teach :

Page 4, lines 6-9 teach labeled polyphosphates can be detected after phosphatase cleavage.

Page 4, lines 12-14 teach a signal can be detected after polymerization and the support and nucleic acid attached to the support can be removed from the reaction mixture.

Page 12, lines 1-10 teach many labels were envisioned as detectable species

Page 13, lines 25-33 teach that following polymerization a signal can be detected.

However, none of the specification that has been cited demonstrates that at time of filing the applicant contemplated a method with that excluded separation by charge of the detectable species or labeled polyphosphate from the reaction mixture. Further the only page 4, lines 12-14 actually talk about separation, but is talking about separating the solid support from the reaction mixture, not the detectable species from the reaction mixture.

The Appellants conclude the arguments directed to the Written description requirement by stating, “that although the specification does not have the negative limitation spelled out literally, it clearly suggests that no separation step is required.” It is emphasized that the issues here is: whether the applicants clearly contemplated a method that excluded the step of separation based on charge and the specification as filed does not support that the applicants contemplated such an invention. Thus contrary to appellants's assertion that the specification provides support for detection without separation based on charge, the cited portions of the specification provides support only for readily distinguishable dyes and dyes that do not require a phosphatase treatment. Therefore the specification does not provide support for "detecting said detectable species without first separating by charge of said detectable species from the reaction mixture” or “detecting said labeled polyphosphate without first separating by charge of said labeled polyphosphate from the reaction mixture".

102(b) rejection of claims 1-7, 9, 11-18, 20-23, 27-38, 40, 42-45, 47, 49-50, 55 and 56 as being anticipated by Williams et al (WO/2001/094609).

Appellants have traversed the rejection of Williams.

The appellants assert that the only change phosphatase treatment brings to the label of Williams is a change in charge, while claim 1 of the instant application the detectable species is generated after phosphatase treatment. This argument has been thoroughly reviewed but is not considered persuasive because the phosphatase treatment of Williams results in a detectable species as claimed.

The appellants further assert that the method “Williams et al. suggests the use of a phosphatase to enhance the charge-switch magnitude of the labeled polyphosphate, the property/detectability of the label in Williams et al. remains the same before and after phosphatase treatment. The only change phosphatase treatment brings to the label in Williams et al. is a change in charge. In comparison, in claim 1 of the instant application, a detectable species is generated after phosphatase treatment.” The brief appears to assert that Williams does not anticipate the claims as Williams teaches the use of a phosphatase. It is noted that claim 1 is a method with comprising language and requires a phosphatase in step (b) and the labeled polyphosphate is detected if a labeled polyphosphate is produced in the polymerization reaction. Williams teaches detection of the released polyphosphate, thus the labeled polyphosphate is detectable (see page 4, lines 20-29). The brief further appears to assert that the claims require that the claims require the generation of a detectable species only after phosphatase treatment, however the claim limitation is “subjecting said reaction mixture to a phosphatase treatment to produce a detectable species if said labeled polyphosphate is produced.” The claim merely requires the detectable species is present after phosphatase treatment. Thus the claims teachings of Williams as stated on page 6 of the brief:

Williams et al. discloses a method for solid phase sequencing of a nucleic acid, which method includes the use of a labeled NP having a detectable moiety, wherein the detectable moiety is released as a charged detectable moiety when the NP is incorporated into the primer. After the application of an energy field, the charged detectable moiety is detected thereby the target nucleic acid sequenced (see e.g. page 4, lines 20-29). Williams et al. teaches that the NP is a nucleoside triphosphate, and the detectable moiety is a gamma-phosphate with a fluorophore attached (see e.g. page 4, lines 14-15). Williams et al. teaches that a phosphatase can be used to enhance "the

charge-switch magnitude by dephosphorylating the PPi-F" (see e.g. page 25, lines 12-13).

The brief further asserts, “Appellants submit that Williams et al. requires a separation by charge of the dye-labeled pyrophosphate product of the polymerase reaction (or the phosphatase treated product, with enhanced charge-switch magnitude) from the dye-labeled nucleotides, prior to detection of the dye (see e.g. Figure 7). This is critical for Williams et al., as the detectable property of the dye (whether as part of the dye- labeled pyrophosphate or the phosphatase treated product) is the same as prior to the polymerase reaction. Without physical separation, it is impossible to distinguish the reaction product from the dye-labeled nucleotide. In claim 1 of the current invention, however, the detectable species generated by phosphatase treatment is readily distinguishable from untreated labeled polyphosphate, or labeled nucleotide, a separation of the dye product (detectable species) from the rest of the reaction components is not necessary. In fact, the labeled nucleotide in the current application is inert to phosphatase treatment, and therefore, phosphatase treatment can be carried out simultaneously with the polymerase reaction (see e.g. page 3, lines 17-31; claim 13).” However Williams teaches:

Upon incorporation by a polymerase, the dNTP is hydrolyzed as usual and the liberated pyrophosphate-dye moiety diffuses into the surrounding medium. The free dye molecule is fluorescent and its appearance is imaged at video-rate under a microscope. A flowing stream sweeps the dye away from the parent DNA molecule. As the polymerase continues to move along the DNA, the nucleotide sequence is read from the order of released dyes. Sequencing proceeds quickly, as fast as the polymerase progresses along the DNA template. (page 22, lines 31 to top of page 23);

In operation, when the enzyme is immobilized, such as a DNA polymerase, the enzyme selects a single DNA molecule from solution. The polymerase incorporates a

first nucleotide at the 3'-end of the primer strand. The polymerase then translocates to the next position on the target DNA, incorporates a complementary nucleotide, and releases the respective PPi-Dye. The released dyes move away from the immobilized enzyme in the flowing sample solution. These events can then be recorded sequentially by video-rateimaging using for example, a CCD camera, capable of detecting single fluorophore molecules. The resulting movie shows the activity of a single polymerase molecule operating on a single molecule of DNA. The nucleotide sequence of the DNA target is read directly from the order of released dyes. When the first nucleic acid molecule has been sequenced, the polymerase releases it and selects another template from solution. Many DNA molecules are thereby sequenced by a single polymerase. The process continues for the life of the enzyme. (page 28, lines 5-10)

Upon incorporation by a polymerase, the dNTP is hydrolyzed as usual and the liberated pyrophosphate-dye moiety diffuses into the surrounding medium. The free dye molecule is fluorescent and its appearance is imaged at video-rate under a microscope. A flowing stream sweeps the dye away from the parent DNA molecule. As the polymerase continues to move along the DNA, the nucleotide sequence is read from the order of released dyes. Sequencing proceeds quickly, as fast as the polymerase progresses along the DNA template. (page 32, lines 20-25).

Thus contrary to the brief's assertions Williams teaches detection without separation by charge. Further the assertion that Williams requires physical separation are not recited in the claim. The claim requires, "detecting said detectable species without first separating by charge of said detectable species from the reaction mixture," which does not exclude other methods of physical separation. Further the response has again implied that the claim requires generation of a detectable species only upon phosphatase treatment, but as discussed above does exclude the species being detectable prior to treatment.

Thus Williams anticipates the claim 1.

Further, these arguments are not considered persuasive as Williams teaches detection of the released polyphosphate, thus the labeled polyphosphate is detectable

(as reproduced previously see page 4, lines 20-29; bottom page 22-top page 23; page 28, lines 5-10; page 32, lines 20-25).

Appellant further asserts, “Appellants submit that Williams et al. require a separation by charge of the dye-labeled pyrophosphate product of the polymerase reaction from the dye-labeled nucleotides, prior to detection (see e.g. Figure 7). This is critical for Williams et al., as the detectable property of the dye is the same as prior to the polymerase reaction. Without physical separation, it is impossible to distinguish the reaction product from the dye-labeled nucleotide. In claim 32 of the current invention, however, the labeled polyphosphate is readily distinguishable from the labeled nucleotide, a separation of the labeled polyphosphate from the rest of the reaction components is not necessary”. This argument has been thoroughly reviewed but is not considered persuasive as the pending claims only exclude separation based on charge and do not exclude any other type of separation such as physical separation. In response to applicant's argument that the references fail to show certain features of applicant’s invention, it is noted that the features upon which applicant relies (i.e., the labeled polyphosphate is detected without physical separation) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Claim 32 does not preclude physical separation of molecules. Further as discussed and reproduced above Williams teaches separation based on diffusion.

The Appellant asserts that the Examiner has mischaracterized the teachings of Williams, as Williams method requires separation by charge. Appellants asserts that nothing on page 24, lines 15-26 suggests the assay can be done without separation by charge. Williams teaches on page 24, lines 15-26"

"The present invention provides a method for detecting pyrophosphate cleavage, the components of the assay comprising a charge-switch NTP, a target nucleic acid, a primer nucleic acid and a polymerase, the method comprising: (a) flowing the labeled charge-switch nucleotide phosphate (NP) having a y-phosphate with a fluorophore moiety attached thereto, past an immobilized component selected from the group consisting of the polymerase and the target nucleic acid; (b) incorporating the NP on a primer strand hybridized to the target nucleic acid using an enzyme and releasing the y-phosphate with the fluorophore moiety attached thereto; and (c) detecting the fluorescent moiety thereby detecting pyrophosphate cleavage. In the methods of the present invention, either the polymerase or the target nucleic acid is attached to a solid phase, such as a solid support."

Williams teaches in bottom page 22-top page 23; page 28, lines 5-10; page 32, lines 20-25 separation by diffusion followed by detection. Appellant appears to be inferring the use of a charge switch nucleotide requires separation by charge in all embodiments, but the examiner has presented 6 teachings by Williams that teach separation by diffusion.

The appellant further asserts that the Williams teaches the labeled polyphosphate is separated by diffusion on page 21, lines 20-25, not page 20. It is noted that a prior art reference is considered as a whole and for all it stands for. The brief continues, "This section, however, clearly states that the PPi-Dye, after diffusion into the medium, is directed by a transverse electric field toward the negative electrode." Thus the Appellant agrees that the dye is separated by diffusion and not separated by charge from the reaction mixture as claimed, the subsequent use of electric filed in

detection is after diffusion from the reaction mixture. The claim does not preclude the use of charge following separation. Further Williams teaches separation based on diffusion:

Upon incorporation by a polymerase, the dNTP is hydrolyzed as usual and the liberated pyrophosphate-dye moiety diffuses into the surrounding medium. The free dye molecule is fluorescent and its appearance is imaged at video-rate under a microscope. A flowing stream sweeps the dye away from the parent DNA molecule. As the polymerase continues to move along the DNA, the nucleotide sequence is read from the order of released dyes. Sequencing proceeds quickly, as fast as the polymerase progresses along the DNA template. (page 22, lines 31 to top of page 23);

In operation, when the enzyme is immobilized, such as a DNA polymerase, the enzyme selects a single DNA molecule from solution. The polymerase incorporates a first nucleotide at the 3'-end of the primer strand. The polymerase then translocates to the next position on the target DNA, incorporates a complementary nucleotide, and releases the respective PPi-Dye. The released dyes move away from the immobilized enzyme in the flowing sample solution. These events can then be recorded sequentially by video-rate imaging using for example, a CCD camera, capable of detecting single fluorophore molecules. The resulting movie shows the activity of a single polymerase molecule operating on a single molecule of DNA. The nucleotide sequence of the DNA target is read directly from the order of released dyes. When the first nucleic acid molecule has been sequenced, the polymerase releases it and selects another template from solution. Many DNA molecules are thereby sequenced by a single polymerase. The process continues for the life of the enzyme. (page 28, lines 5-10)

Upon incorporation by a polymerase, the dNTP is hydrolyzed as usual and the liberated pyrophosphate-dye moiety diffuses into the surrounding medium. The free dye molecule is fluorescent and its appearance is imaged at video-rate under a microscope. A flowing stream sweeps the dye away from the parent DNA molecule. As the polymerase continues to move along the DNA, the nucleotide sequence is read from the order of released dyes. Sequencing proceeds quickly, as fast as the polymerase progresses along the DNA template. (page 32, lines 20-25).

Thus Williams et anticipates the limitations of the instant claims.

Claims 8 and 39

The appellant asserts that Williams does not disclose the independent invention of claims 1 and 32, the combination of Williams and Wittwer does not render claims 8

and 39 obvious. The arguments directed to Williams have been addressed above. As no arguments have been presented to the combination of Williams and Wittwer, this rejection is proper and maintained.

Claims 10 and 41

The appellant asserts that Williams does not disclose the independent invention of claims 1 and 32, the combination of Williams and Keller does not render claims 10 and 41 obvious. The arguments directed to Williams have been addressed above. As no arguments have been presented to the combination of Williams and Keller, this rejection is proper and maintained.

Claims 19 and 46

The appellant asserts that Williams does not disclose the independent invention of claims 1 and 32, the combination of Williams and Lichenwalter does not render claims 19 and 46 obvious. The arguments directed to Williams have been addressed above. As no arguments have been presented to the combination of Williams and Lichenwalter, this rejection is proper and maintained.

Claims 23-25

The appellant asserts that Williams does not disclose the independent invention of claims 1 and 32, the combination of Williams and Hattori does not render claims 23-25 obvious. The arguments directed to Williams have been addressed above. As no arguments have been presented to the combination of Williams and Hattori, this rejection is proper and maintained.

Claims 25 and 26

The appellant asserts that Williams does not disclose the independent invention of claims 1 and 32, the combination of Williams and Bronstein does not render claims 25 and 26 obvious. The arguments directed to Williams have been addressed above. As no arguments have been presented to the combination of Williams and Bronstein, this rejection is proper and maintained.

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Steven Pohnert

/Steven C Pohnert/

Examiner, Art Unit 1634

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